



**BILLING CODE 4163-18-P**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**42 CFR Part 88**

**[NIOSH Docket 094]**

**World Trade Center Health Program; Petition 023—Uterine Cancer, Including Endometrial Cancer; Finding of Insufficient Evidence**

**AGENCY:** Centers for Disease Control and Prevention, HHS.

**ACTION:** Denial of petition for addition of a health condition.

**SUMMARY:** On April 23, 2019, the Administrator of the World Trade Center (WTC) Health Program received a petition (Petition 023) to add “endometrial cancer” to the List of WTC-Related Health Conditions (List). Upon reviewing the scientific and medical literature, including information provided by the petitioner, the Administrator has determined that the available evidence does not have the potential to provide a basis for a decision on whether to add the major site uterine cancer, including its subtype, endometrial cancer, to the List. The Administrator also finds that insufficient evidence exists to request a recommendation of the WTC Health Program Scientific/Technical Advisory Committee (STAC), to publish a proposed rule, or to publish a determination not to publish a proposed rule.

**DATES:** The Administrator of the WTC Health Program is denying this petition for the addition of a health condition as of [INSERT DATE OF PUBLICATION IN **FEDERAL REGISTER**].

**ADDRESSES:** Visit the WTC Health Program website at

<https://www.cdc.gov/wtc/received.html> to review Petition 023.

**FOR FURTHER INFORMATION CONTACT:** Rachel Weiss, Program Analyst,

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**SUPPLEMENTARY INFORMATION:**

**Table of Contents**

A. WTC Health Program Statutory Authority

B. Procedures for Evaluating a Petition for Cancer

C. Petition 023

D. Assessment of Scientific and Medical Information

E. Administrator's Final Decision on Whether to Propose the Addition of Uterine Cancer, Including Endometrial Cancer, to the List

F. Approval to Submit Document to the Office of the Federal Register

**A. WTC Health Program Statutory Authority**

Title I of the James Zadroga 9/11 Health and Compensation Act of 2010 (Pub. L. 111-347, as amended by Pub. L. 114-113), added Title XXXIII to the Public Health Service (PHS) Act,<sup>1</sup> establishing the WTC Health Program within the Department of Health and Human Services (HHS). The WTC Health Program provides medical monitoring and treatment benefits for health conditions on the List to eligible firefighters and related personnel, law enforcement officers, and rescue, recovery, and cleanup workers who responded to the September 11, 2001, terrorist attacks in New York City, at the Pentagon, and in Shanksville, Pennsylvania (responders), and to eligible persons who were present in the dust or dust cloud on September 11, 2001, or who worked, resided, or

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<sup>1</sup> Title XXXIII of the PHS Act is codified at 42 U.S.C. 300mm to 300mm-61. Those portions of the James Zadroga 9/11 Health and Compensation Act of 2010 found in Titles II and III of Public Law 111-347 do not pertain to the WTC Health Program and are codified elsewhere.

attended school, childcare, or adult daycare in the New York City disaster area (survivors).

All references to the Administrator of the WTC Health Program (Administrator) in this document mean the Director of the National Institute for Occupational Safety and Health (NIOSH) or his designee.

Pursuant to section 3312(a)(6)(B) of the PHS Act, interested parties may petition the Administrator to add a health condition to the List in 42 CFR 88.15. Within 90 days after receipt of a valid petition to add a condition to the List, the Administrator must take one of the following four actions described in section 3312(a)(6)(B) of the PHS Act and § 88.16(a)(2) of the Program regulations: (1) Request a recommendation of the STAC, (2) publish a proposed rule in the *Federal Register* to add such health condition, (3) publish in the *Federal Register* the Administrator's determination not to publish such a proposed rule and the basis for such determination, or (4) publish in the *Federal Register* a determination that insufficient evidence exists to take action under (1) through (3) above.

## **B. Procedures for Evaluating a Petition for Cancer**

In addition to the regulatory provisions, the WTC Health Program has developed policies to guide the review of submissions and petitions,<sup>2</sup> as well as the analysis of evidence supporting the potential addition of a type of cancer to the List.<sup>3</sup>

A valid petition must include sufficient medical basis for the association between the September 11, 2001, terrorist attacks and the health condition to be added; in

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<sup>2</sup> See WTC Health Program [2014], *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions*, May 14, 2014, <http://www.cdc.gov/wtc/pdfs/WTCHPPPPetitionHandlingProcedures14May2014.pdf>.

<sup>3</sup> See WTC Health Program [2019], *Policy and Procedures for Adding Types of Cancer to the List of WTC-Related Health Conditions*, May 1, 2019, [https://www.cdc.gov/wtc/pdfs/policies/WTCHP\\_PP\\_Addition\\_of\\_Cancer\\_Policy\\_UPDATED\\_050719-508.pdf](https://www.cdc.gov/wtc/pdfs/policies/WTCHP_PP_Addition_of_Cancer_Policy_UPDATED_050719-508.pdf).

accordance with WTC Health Program policy, reference to a peer-reviewed, published, epidemiologic study about the health condition among 9/11-exposed populations or to clinical case reports of health conditions in WTC responders or survivors may demonstrate the required medical basis.<sup>4</sup> Studies linking 9/11 agents<sup>5</sup> or hazards to the petitioned health condition may also provide sufficient medical basis for a valid petition.

After the Program has determined that a petition is valid, the Administrator must direct the Program to conduct a systematic literature search (a keyword search of relevant scientific databases) to gather information about the following: (1) studies about the type of cancer requested to be added to the List among 9/11-exposed populations, (2) studies showing a potential causal association between the requested cancer and a health condition on the List, and (3) classifications of the World Health Organization's International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) *Report on Carcinogens* relevant to the requested cancer. Peer-reviewed, published, epidemiologic studies of the cancer in 9/11-exposed populations are considered relevant. The quantity and quality of relevant studies are reviewed for their potential to provide a basis for deciding whether to propose adding the type of cancer to the List.

If the Program determines that the relevant studies have the potential to provide a basis for deciding whether to propose adding the type of cancer to the List, the cancer type may be added to the List if one of the four following methods is met:

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<sup>4</sup> See *supra* note 2.

<sup>5</sup> 9/11 agents are chemical, physical, biological, or other hazards reported in a published, peer-reviewed exposure assessment study of responders, recovery workers, or survivors who were present in the New York City disaster area, or at the Pentagon site, or the Shanksville, Pennsylvania site, as those locations are defined in 42 CFR 88.1, as well as those hazards not identified in a published, peer-reviewed exposure assessment study, but which are reasonably assumed to have been present at any of the three sites. See WTC Health Program [2018], *Development of the Inventory of 9/11 Agents*, July 17, 2018, [https://wwwn.cdc.gov/ResearchGateway/Content/pdfs/Development\\_of\\_the\\_Inventory\\_of\\_9-11\\_Agents\\_20180717.pdf](https://wwwn.cdc.gov/ResearchGateway/Content/pdfs/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf).

***Method 1. Epidemiologic Studies of September 11, 2001-Exposed Populations.***

The peer-reviewed, published, epidemiologic studies of 9/11-exposed populations are assessed by applying the following criteria extrapolated from the Bradford Hill criteria, as appropriate:

- a. Strength of the association between a 9/11 exposure and a type of cancer (including the precision of the risk estimate<sup>6</sup>),
- b. Consistency of the findings across multiple studies. If only a single published epidemiologic study is available for assessment, the consistency of findings cannot be evaluated and more emphasis will be placed on evaluating the strength of the association and the precision of the risk estimate,
- c. Biological gradient, or dose-response relationships between 9/11 exposures and the type of cancer, and
- d. Plausibility and coherence with known facts about the biology of the type of cancer.

***Method 2. Established Causal Associations.***

A type of cancer may be added to the List if there is well-established scientific support published in multiple epidemiologic studies for a causal association between that cancer and a condition already on the List of WTC-Related Health Conditions.

***Method 3. Review of Evaluations of Carcinogenicity in Humans.***

A type of cancer may be added to the List under Method 3 if both of the following criteria are satisfied:

**3A. Published Exposure Assessment Information.** A 9/11 agent included in the *Inventory of 9/11 Agents*<sup>7</sup> is identified, and

**3B. Evaluation of Carcinogenicity in Humans from Scientific Studies.** NTP has determined that the [identified] 9/11 agent is *known to be a human carcinogen* or is *reasonably anticipated to be a human carcinogen*, and IARC has determined there is *sufficient* or *limited* evidence that the 9/11 agent causes [the requested] type of cancer.

***Method 4. Review of Information Provided by the WTC Health Program Scientific/Technical Advisory Committee.***<sup>8</sup>

A type of cancer may be added to the List if the STAC has provided a reasonable basis for adding a type of cancer.

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<sup>6</sup> A precision of the risk estimate describes the uncertainty inherent in estimating the strength of association (the effect size) between exposure and health effect from observational data. It is expressed as a confidence interval illustrating a range of values that contains the true effect size. A narrow confidence interval indicates a more precise measure of the effect size and a wider interval indicates greater uncertainty.

<sup>7</sup> The *Inventory of 9/11 Agents* is composed of those agents identified in Tables 1-4 of the document, *Development of the Inventory of 9/11 Agents*. See *supra* note 5.

<sup>8</sup> The WTC Health Program Scientific/Technical Advisory Committee may be convened by the Administrator if he determines that its advice would be helpful. See *supra* note 3 at Sec. V.

If the evaluation of evidence required for any of the four methods demonstrates that the criteria in that method are satisfied, the Administrator will propose the addition of the type of cancer to the List.

### **C. Petition 023**

On April 23, 2019, the Administrator received a petition (Petition 023) requesting the addition of “endometrial cancer” to the List.<sup>9</sup> The petition included a 2002 study by Lioy *et al.*<sup>10</sup> and a 2017 study by McElroy *et al.*<sup>11</sup> which together provided sufficient medical basis for the petition to be considered valid because they demonstrate the presence of 9/11 agents, including cadmium, at the WTC site and that cadmium exposure is associated with a statistically significant increase in endometrial cancer risk. However, because neither Lioy *et al.* [2002] nor McElroy *et al.* [2017] is a peer-reviewed, published, epidemiologic study of endometrial cancer (or the major site, uterine cancer) in a 9/11-exposed population, neither study is considered relevant nor are they further reviewed in this action.

In the Program’s List of WTC-Related Health Conditions, types of cancer are identified by the major cancer site/histology groups that are commonly used in the reporting of cancer incidence data, using the groupings standardized by the National Cancer Institute’s Surveillance, Epidemiology and End Results Program (SEER) for

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<sup>9</sup> See Petition 023, *WTC Health Program: Petitions Received*, <http://www.cdc.gov/wtc/received.html>.

<sup>10</sup> Lioy PJ, Weisel CP, Millette JR, Eisenreich S, Vallero D, Offenberg J, Turpin B, Zhong M, Cohen MD, Prophete C, Yang I, Stiles R, Chee G, Johnson W, Porcja R, Alimokhtari S, Hale RC, Weschler C, Chen LC [2002], *Characterization of the Dust/Smoke Aerosol that Settled East of the World Trade Center (WTC) in Lower Manhattan after the Collapse of the WTC11 September 2001*, *Environ Health Perspect* 110(7), 703-714.

<sup>11</sup> McElroy JA, Kruse RL, Guthrie J, Gangnon RE, Robertson JD [2017], *Cadmium Exposure and Endometrial Cancer Risk: A Large Midwestern U.S. Population-Based Case-Control Study*, *PLoS ONE* 12(7): e0179360.

national cancer surveillance.<sup>12</sup> Cancer subtypes are not included in the List. Because endometrial cancer is a subtype of uterine cancer,<sup>13</sup> the Program has determined that the scope of this petition and subsequent Program review should include both endometrial cancer and the major site, uterine cancer.

#### **D. Assessment of Scientific and Medical Information**

In response to Petition 023, the Program conducted both a systematic literature search to identify peer-reviewed, published studies of uterine cancer, including endometrial cancer, in 9/11-exposed women, as well as a review of NTP and IARC classifications of 9/11 agents, including those 9/11 agents identified by IARC as carcinogenic agents with *sufficient* or *limited* evidence that the agent causes uterine cancer, including endometrial cancer, in humans.<sup>14</sup> The National Cancer Institute has not identified any of the health conditions on the List of WTC-Related Health Conditions as known risk factors for uterine or endometrial cancer; therefore, a systematic literature search for studies regarding a causal association between uterine or endometrial cancer and a health condition on the List was not conducted.<sup>15</sup>

#### *Literature Search Results*

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<sup>12</sup> National Cancer Institute [2008], Surveillance Epidemiology and End Results: Site Recode ICD-O-3/WHO 2008 Definition, [https://seer.cancer.gov/siterecode/icdo3\\_dwho/home/index.html/](https://seer.cancer.gov/siterecode/icdo3_dwho/home/index.html/).

<sup>13</sup> Endometrial cancer develops in the lining of the uterus, called the endometrium. Although endometrial uterine cancer is the most common type of uterine cancer, accounting for more than 90 percent of cases, there are other types of uterine cancer. *See* <https://www.cancer.gov/types/uterine/patient/endometrial-treatment-pdq>.

<sup>14</sup> Databases searched include: CINAHL, Embase, NIOSHTIC-2, ProQuest Health & Safety, PsycINFO, Ovid MEDLINE, Scopus, Toxicology Abstracts/TOXLINE, and WTC Health Program Bibliographic Database. Keywords used to conduct the search include: endometrial neoplasm, endometrial cancer, endometrial carcinoma, malignant neoplasm of endometrium, adenocarcinoma of endometrium, cancer of the endometrium, Uterine Neoplasm, malignant neoplasm of corpus uteri, uterine cancer, uterine carcinoma. The literature search was conducted in English-language journals on May 23, 2019.

<sup>15</sup> No health conditions on the List of WTC-Related Health Conditions are known risk factors for uterine cancer. *See* <https://www.cancer.gov/types/uterine/hp/endometrial-prevention-pdq>.

Two publications were identified in the search for studies specifically regarding uterine cancer, including endometrial cancer, among 9/11-exposed populations, thus meeting the Program’s criteria for further evaluation: Li *et al.* [2012]<sup>16</sup> and its update Li *et al.* [2016].<sup>17</sup> In addition to the two Li *et al.* publications found in the literature search, the Program was aware of additional studies examining all types of cancer in 9/11-exposed subpopulations (rescue and recovery workers and survivors); these additional studies were also reviewed to determine whether they may provide further insight into cancer incidence and mortality applicable to the evaluation of uterine cancer, including endometrial cancer: Jordan *et al.* [2011]<sup>18</sup> and its update Jordan *et al.* [2018],<sup>19</sup> Zeig-Owens *et al.* [2011]<sup>20</sup> and its update Moir *et al.* [2016],<sup>21</sup> Solan *et al.* [2013],<sup>22</sup> Kleinman *et al.* [2015],<sup>23</sup> and Stein *et al.* [2016].<sup>24</sup> Of the additional studies, only Zeig-Owens *et al.* [2011] and its update Moir *et al.* [2016] were found not to be relevant (they were not peer-reviewed, published, studies of uterine or endometrial cancer in the 9/11-exposed population) because neither addressed cancers in female WTC responders. The other five

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<sup>16</sup> Li J, Cone JE, Kahn AR, Brackbill RM, Farfel MR, Greene CM, Hadler JL, Stayner LT, Stellman SD [2012], *Association between World Trade Center Exposure and Excess Cancer Risk*, JAMA 308(23):2479–88.

<sup>17</sup> Li J, Brackbill RM, Liao TS, Qiao B, Cone JE, Farfel MR, Hadler JL, Kahn AR, Konty KJ, Stayner LT, Stellman SD [2016], *Ten-Year Cancer Incidence in Rescue/Recovery Workers and Civilians Exposed to the September 11, 2001 Terrorist Attacks on the World Trade Center*, Am J Ind Med 59(9):709–21.

<sup>18</sup> Jordan HT, Brackbill RM, Cone JE, Debcoudhury I, Farfel MR, Greene CM, Hadler JL, Kennedy J, Li J, Liff J, Stayner L, Stellman SD [2011], *Mortality among Survivors of the Sept 11, 2001, World Trade Center Disaster: Results from the World Trade Center Health Registry Cohort*, Lancet 378(9794):879–87.

<sup>19</sup> Jordan HT, Stein CR, Li J, Cone JE, Stayner L, Hadler JL, Brackbill RM, Farfel MR [2018], *Mortality among Rescue and Recovery Workers and Community Members Exposed to the September 11, 2001 World Trade Center Terrorist Attacks, 2003-2014*, Environ Res 163:270–9.

<sup>20</sup> Zeig-Owens R, Webber MP, Hall CB, Schwartz T, Jaber N, Weakley J, Rohan TE, Cohen HW, Derman O, Aldrich TK, Kelly K, Prezant DJ [2011], *Early Assessment of Cancer Outcomes in New York City Firefighters after the 9/11 Attacks: an Observational Cohort Study*, Lancet 378(9794):898–905.

<sup>21</sup> Moir W, Zeig-Owens R, Daniels RD, Hall CB, Webber MP, Jaber N, Yiin JH, Schwartz T, Liu X, Vossbrinck M, Kelly K, Prezant D [2016], *Post-9/11 Cancer Incidence in World Trade Center-Exposed New York City Firefighters as Compared to a Pooled Cohort of Firefighters from San Francisco, Chicago and Philadelphia (9/11/2001-2009)*, Am J Ind Med 59(9):722–30.

<sup>22</sup> Solan S, Wallenstein S, Shapiro M, Teitelbaum SL, Stevenson L, Kochman A, Kaplan J, Dellenbaugh C, Kahn A, Biro FN, Crane M, Crowley L, Gabrilove J, Gonsalves L, Harrison D, Herbert R, Luft B, Markowitz SB, Moline J, Niu X, Sacks H, Shukla G, Udasin I, Lucchini RG, Boffetta P, Landrigan PJ [2013], *Cancer Incidence in World Trade Center Rescue and Recovery Workers, 2001-2008*, Environ Health Perspect 21(6):699–704.

<sup>23</sup> Kleinman EJ, Christos PJ, Gerber LM, Reilly JP, Moran WF, Einstein AJ, Neugut AI [2015], *NYPD Cancer Incidence Rates 1995-2014 Encompassing the Entire World Trade Center Cohort*, J Occup Environ Med 57(10):e101–13.

<sup>24</sup> Stein CR, Wallenstein S, Shapiro M, Hashim D, Moline JM, Udasin I, Crane MA, Luft BJ, Lucchini RG, Holden WL [2016], *Mortality among World Trade Center Rescue and Recovery Workers, 2002-2011*, Am J Ind Med 59(2):87–95.



additional studies, along with Li *et al.* [2012] and Li *et al.* [2016], were found to be relevant and were reviewed for quantity and quality, below.

The Program reviewed the NTP *Report on Carcinogens*<sup>25</sup> and found that twelve 9/11 agents<sup>26</sup> are *known to be human carcinogens* and twenty-seven 9/11 agents are *reasonably anticipated to be human carcinogens*.<sup>27</sup> However, IARC has not determined that any of these thirty-nine 9/11 agents demonstrate *sufficient* or *limited* evidence of a causal association with uterine or endometrial cancer in humans.<sup>28</sup>

### *Review of Relevant Studies*

The studies identified as relevant during the literature review process were further assessed to determine whether they have sufficient quality and quantity to demonstrate a potential to support the addition of uterine cancer, including endometrial cancer. The relevant studies introduced above are described below, including a description of their respective strengths and limitations.

Jordan *et al.* [2011] conducted a mortality study among the cohort of WTC Health Registry enrollees that included 13,337 rescue/recovery workers (3,188 women) and 28,593 survivors (16,733 women) living in New York City at the time of their enrollment. The authors identified deaths occurring in 2003-2009 through linkage to New

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<sup>25</sup> National Toxicology Program, HHS [2016], *Report on Carcinogens*, 14<sup>th</sup> Edition (Research Triangle Park, NC). <https://ntp.niehs.nih.gov/go/roc14>.

<sup>26</sup> As identified in the *Inventory of 9/11 Agents*, see *supra* notes 7 and 5.

<sup>27</sup> The 39 total 9/11 agents identified by NTP are as follows: Arsenic, Asbestos, Benzene, Beryllium, 1,3-Butadiene, Cadmium, Nickel, Silica, Solar Radiation, Soot, Sulfuric Acid, Trichloroethylene (*Known To Be Human Carcinogens*); as well as Acetaldehyde, Acrylonitrile, Benz[a]anthracene, Benzo[k]fluoranthene, Benzo[a]pyrene, Carbon Tetrachloride, Chloroform, Cobalt, Dibenz[a,h]anthracene, 1,4-Dichlorobenzene, Dichlorodiphenyltrichloroethane, 1,2-Dichloroethane, Dichloromethane, 1,3-Dichloropropene, Diesel Exhaust Particulates, 1,4-Dioxane, Hexachlorobenzene, Lead, Hexachlorocyclohexane, Mirex, Naphthalene, Nickel, Polybrominated Biphenyls, Polychlorinated Biphenyls, Styrene, Tetrachloroethylene, and Toluene Diisocyanates (*Reasonably Anticipated To Be Human Carcinogens*).

<sup>28</sup> International Agency for Research on Cancer [1976], *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man: Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anesthetics*, Volume 11; Lyon, France.

York City vital records and the National Death Index (NDI). Standardized mortality ratios (SMRs) were calculated with New York City rates from 2000 to 2009 as the reference. Within the cohort, proportional hazards were used to examine the relation between WTC-related exposure levels (high, intermediate, or low for each group, based on exposure to the dust cloud, and time and duration working on the pile) and all-cause mortality, but not mortality for specific cancers. All-cause SMRs were significantly lower than that expected for rescue/recovery workers (SMR=0.45, 95% CI (confidence interval) 0.38-0.53) and survivors (SMR=0.61, 95% CI 0.56-0.66). There were no significantly elevated SMRs for any category of cancer examined, including cancer of female genital organs, among all studied Registry enrollees (SMR=0.82, 95% CI 0.49-1.28), rescue/recovery workers (SMR=0.67, 95% CI 0.08-2.43), or survivors (SMR=0.84, 95% CI 0.49-1.35). Separate SMRs for cancer of specific types of female genital organs, including uterine cancer, were not provided. SMRs were adjusted for age, sex, race, and calendar year. Adjusted hazard ratios (AHRs) were adjusted for age, sex, race and ethnic origin, income, smoking, and, for survivors, Registry recruitment source. This study's limitations include possible selection bias, since enrollment in the Registry is voluntary. Exposure reporting may also be subject to recall error because 9/11 exposures were self-reported 2 to 3 years after the September 11, 2001 terrorist attacks and subsequent clean-up of the sites. The healthy worker effect puts the population of rescue/recovery workers at a lower risk of cancer compared to the general population,<sup>29</sup> which includes persons who are chronically ill, hospitalized, or otherwise unemployable. In addition, other

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<sup>29</sup> The healthy worker effect is a form of selection bias "typically seen in observational studies of occupational exposures with improper choice of comparison group (usually general population)." See Chowdhury R, Shah D, Payal AR, [2017], *Healthy Worker Effect Phenomenon: Revisited with Emphasis on Statistical Methods – A Review*, Indian J Occup Environ Med 21(1), 2-8.

potential confounders, such as family cancer history and occupational exposures prior to September 11, 2001, were not measured.

Jordan *et al.* [2018] updated their 2011 study, discussed above, by including the full cohort of WTC Health Registry enrollees, not only those living in New York City at time of enrollment, and adding 5 years of follow-up. The 2018 update included 29,280 rescue/recovery workers (6,422 women) and 39,643 survivors (21,126 women). The authors used New York City population mortality rates from 2003 to 2012 as the primary reference, and also conducted a secondary analysis using U.S. population comparison rates from 2003 to 2011. Proportional hazards were used to examine the relation between WTC-related exposure levels (high, intermediate, or low for each group, based on time and duration in lower Manhattan) and total mortality, as well as overall cancer mortality, but not mortality for specific cancer types. Overall cancer SMRs were not elevated for rescue/recovery workers (SMR=0.94, 95% CI 0.84-1.05), but were significantly elevated among survivors (SMR=1.14, 95% CI 1.06-1.24) when compared to the New York City population; no elevated SMRs were reported for all cancers using the general U.S. population as reference. Cancers of the female genital organs were not significantly elevated among rescue/recovery workers or survivors (observed deaths=7, SMR=0.67, 95% CI 0.27-1.39 and observed deaths=43, SMR=1.17, 95% CI 0.85-1.58, respectively). The authors also examined 119 sub-categories of the major causes of death, but only reported statistically significant results; uterine cancers were not among the reported causes of death, suggesting that the risk of uterine cancer was not significantly elevated. No statistically significant elevations and no significant trends were observed in the analyses of the association between WTC-related exposures and overall cancer mortality.

Like the previously reviewed study, Jordan *et al.* [2018] is prone to selection bias, because enrollment in the Registry was voluntary. Further, 9/11 exposures were self-reported 2 to 3 years after the September 11, 2001 terrorist attacks, and thus are subject to recall error. The healthy worker effect may put the population of rescue/recovery workers at a lower risk of cancer compared with the general population. An analogous effect has been seen in people who volunteer for health studies and might have contributed to the low relative mortality in both the rescue/recovery and survivor participants. As in the previously described study, other potential confounders, such as family cancer history and occupational exposures prior to September 11, 2001, were not measured.

Li *et al.* [2012] conducted a cancer incidence study among enrollees in the WTC Health Registry who were residents of New York State on September 11, 2001, and had no history of cancer at the time of enrollment. A total of 55,778 individuals were eligible for the study, including 21,850 involved in rescue/recovery (4,185 women) and 33,928 survivors not involved in rescue/recovery (18,922 women). The authors identified cancers by linkage to 11 state cancer registries based on the state of residence of the cohort member, and based expected numbers of cancers on New York State cancer rates. They used qualitative descriptions of 9/11 exposures to classify Registry enrollee exposure as high, intermediate, or low based on time and duration in lower Manhattan. The authors conducted separate analyses for rescue/recovery workers and for survivors, and presented separate results for the period of enrollment through 2006 (early period) and 2007 through 2008 (later period). Among rescue/recovery workers, the standardized

incidence ratio (SIR)<sup>30</sup> for all cancer sites combined was not statistically significantly elevated in either period (early period, SIR=0.94; 95% CI, 0.82-1.08; later period SIR=1.14; 95% CI, 0.99-1.30). Uterine cancer incidence was not elevated for rescue/recovery workers during the early period (five cases or less [the precise number of cases was not reported, likely because of restrictions on reporting small numbers], SIR=0.97, 95% CI 0.2-2.83), and no cases were reported during the later period. Among survivors, no significantly increased incidence for all cancer sites combined was observed in either period. Uterine cancer incidence was not elevated for survivors during the early or late periods (early: observed uterine cancers=16, SIR=1.01, 95% CI 0.58-1.65 and late: observed uterine cancers=14, SIR=1.01, 95% CI 0.55-1.69, respectively). Results of analyses to assess the risk of uterine cancer as a function of 9/11 exposure levels were not reported. SIRs were stratified by age (5-year age groups), race/ethnicity, sex, and calendar period (2003-2006 and 2007-2008). Exposure covariates included age at enrollment, sex, race/ethnicity, 2002 household income level, education level, smoking status, enrollment source (identified by employers, government agencies, and other entities or by an outreach campaign), and history of asthma, cardiovascular disease, stroke, emphysema, or diabetes reported at enrollment. But other potential confounders, such as family cancer history and occupational exposures prior to September 11, 2001, were not measured. The study by Li *et al.* [2012] is prone to selection bias because enrollment in the Registry was voluntary. The authors attempted to mitigate this bias by restricting the analyses to individuals without prior invasive cancer history documented in any of the 11 state cancer registries and focusing on cancer incidence from 2007 to

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<sup>30</sup> SIR is a mathematical expression that compares the incidence experience between the population under study and the experience of that population had they had the same incidence experience of a comparison population.

2008. Self-reported 9/11 exposures may be subject to recall error. Cancer cases identified through linkages with state cancer registries might be underestimated, especially among those without a known Social Security number because a percentage of Registry enrollees did not provide one. The findings on rescue/recovery workers may also be prone to the healthy worker effect.

Li *et al.* [2016] updated their 2012 study, discussed above, which evaluated excess cancer among WTC Health Registry enrollees. In the 2016 update, the authors added 3 years of follow-up to allow for 10 years of cancer latency since the WTC-related exposures. The 2016 study recalibrated the definition of “WTC disaster physical exposures” to emphasize potential contaminants containing carcinogens. The analysis focused on cancers occurring from 2007 through 2011. The study included a total of 60,339 eligible individuals, including 24,863 rescue/recovery workers (5,015 women) and 35,476 survivors not involved in rescue/recovery (18,845 women). The authors identified cancers by linkage to 11 state cancer registries based on the state of residence of the cohort member, and based expected numbers of cancers on overall New York State rates and person-years of follow-up during 2007–2011, adjusted for age (5-year groups), race/ethnicity, sex, and calendar period (2007–2011). The study found that overall cancer incidence was significantly greater than the reference (non-9/11-exposed) population among both rescue/recovery workers (SIR=1.11, 95% CI 1.03-1.20) and survivors (SIR=1.08, 95% CI 1.02-1.15). Uterine cancer incidence was not significantly elevated among rescue/recovery workers nor among survivors (observed uterine cancers=8, SIR=0.82, 95% CI 0.35-1.62 and observed uterine cancers=37, SIR=1.03, 95% CI 0.72-1.41, respectively). Comparisons among exposure groups were not reported for uterine

cancer. In internal analyses, hazard ratios and 95% CI were adjusted for age at enrollment, sex, race/ethnicity, smoking, education, income, and history of a serious non-malignant medical condition; however, findings for uterine cancer were not reported. Other potential confounders were not measured. This study was prone to selection bias, because enrollment in the Registry was voluntary; the authors attempted to mitigate this bias by restricting the analyses to individuals without prior invasive cancer history documented in any of the 11 state cancer registries and focusing on cancer incidence from 2007 through 2011. In addition, findings on rescue/recovery workers may also be subject to the healthy worker effect.

Solan *et al.* [2013] conducted a cancer incidence study among 20,984 non-FDNY WTC Health Program members (3,203 women) involved in rescue, recovery, and cleanup efforts at Ground Zero after 9/11. The authors identified cancer cases through linkage with the tumor registries in the four states in which 98 percent of WTC responders resided at time of enrollment in the Program. Self-reported exposures were categorized based on four variables: pre-September 11, 2001 occupation, extent of exposure to the dust cloud on September 11, 2001, duration of time spent working at the site, and work on the debris pile during four periods (September 2001, October 2001, November-December 2001, and January-June 2002). An integrated exposure variable was created using a 4-point scale (very high, high, intermediate, and low) based on total time spent working at Ground Zero, exposure to the dust cloud, and work on the debris pile. The authors obtained vital status through linkage with the NDI and next-of-kin reports. Expected numbers of cancer cases were calculated based on state rates (for New York, New Jersey, and Connecticut residents) and national rates (for Pennsylvania residents)

according to age (in 5-year groups), sex, and race/ethnicity for each year at risk. The observed and expected numbers of cancers were used to calculate SIRs. The SIR among study participants was elevated and statistically significant for all cancer sites combined (SIR=1.15; 95% confidence interval (CI), 1.06-1.25). Fewer than six cases of uterine cancer were observed, and no additional information was reported for this type of cancer. Furthermore, no SIRs were reported for uterine cancer nor were risk ratios reported for the association between 9/11 exposure variables and uterine cancer. Certain potential confounders, such as family cancer history, were not measured. The study is also prone to selection bias, because enrollment in the WTC Health Program is voluntary. Although the authors used all available exposure metrics, relative risk was not reported for the association between 9/11 exposure variables and uterine cancer. This study may also be subject to the healthy worker effect, which puts this population at a lower risk of cancer compared to the general population.

Kleinman *et al.* [2015] investigated cancer incidence in 39,946 police officers employed by the New York City Police Department (NYPD) on September 11, 2001 (6,366 women), followed during the time periods 1995 to 2000 and 2002 to 2014. The authors reported a 44 percent increase in the overall median age-adjusted incidence rate for all cancers, but no increase in the overall median age-adjusted incidence rates for either malignant neoplasms of the uterus, unspecified part (based on two cases diagnosed pre-9/11 and zero cases diagnosed post-9/11) or uterine adenocarcinomas (based on zero cases diagnosed pre-9/11 and three cases post-9/11). This study is limited by the inherent problems with its design (*i.e.*, the effects of age, time period, and cohort parameters are intertwined in a manner which complicates study interpretation); the study is further



limited by the small number of cancer cases observed as well as the absence of information regarding participants' presence in the dust cloud and the dates and duration of their 9/11 exposures.

Stein *et al.* [2016] conducted a mortality study of 28,918 rescue/recovery workers (4,286 women) enrolled in the WTC Health Program between July 16, 2002, and December 31, 2011. The authors were aware that 16,177 WTC responders were alive due to follow-up visits after the end of 2011, and therefore linked the remainder (n=12,741) to the National Death Index (NDI). Mortality information from the NDI was supplemented by next-of-kin report. Similar to the study by Solan *et al.* [2013], discussed above, the authors of this study created an integrated exposure variable using a 4-point scale (very high, high, intermediate, and low) based on total time spent working at Ground Zero, exposure to the dust cloud, and work on the debris pile. SMRs were standardized for age (5-year groups), sex, race, and calendar year to compare all-cause and cause-specific mortality among responders with mortality in the U.S. general population. Hazard ratios were adjusted for age on September 11, 2001, pre-September 11, 2001 occupation, sex, race/ethnicity, year of WTC Health Program enrollment, smoking, and measured body mass index. Overall mortality in this cohort was statistically significantly decreased (SMR=0.43; 95% CI, 0.39-0.48), although an overall cancer SMR was not reported. Most cancer site-specific SMRs were significantly decreased; however, the SMR for cancer of the female genital organs was decreased but was not statistically significant (SMR=0.65, 95% CI 0.08-2.37) and was based on only two deaths. An SMR for uterine cancer was not provided, neither were hazard ratios for the association between WTC-related exposure variables and mortality from uterine cancer. Some potential confounders, such

as family cancer history, were not measured. The study is prone to selection bias because enrollment in the WTC Health Program was voluntary. Social Security numbers were available for only 37 percent of the records sent to NDI for linkage, limiting the quality of the matches. The healthy worker effect may put this population at a lower risk of cancer compared to the general population.

### *Quantity and Quality Review of Relevant Studies*

The quantity and quality of these seven studies were reviewed together to examine whether the available evidence has the potential to provide a basis for a decision on whether to add uterine cancer, including endometrial cancer, to the List. Prospective cohort studies, like those described above, have the advantage that study participants are considered to be disease-free at the beginning of the observation period when their exposure occurred; therefore, in such studies it is often possible to establish the temporal sequence between exposure and outcome. Cancer studies, however, present unique concerns since some cancers become apparent only after long periods of time following exposure.<sup>31</sup> This latency effect means it is possible that a cancer may have been present but undetected prior to September 11, 2001. In addition, all of the studies described above have had a relatively short period of follow-up since September 11, 2001.

The size and makeup of the cohorts studied may also limit the usefulness of the studies. The studies discussed above may not have the necessary statistical power to detect excesses in uterine cancer, due to the small number of females in the cohort. This

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<sup>31</sup> This delay between environmental exposure and onset of cancer symptoms is referred to as the “cancer latency period.” For more information about latency for cancers and how the WTC Health Program has addressed this issue, please see *Minimum Latency & Types or Categories of Cancer*, Jan. 6, 2015, <https://www.cdc.gov/wtc/pdfs/policies/WTCHP-Minimum-Cancer-Latency-PP-01062015-508.pdf>.

is especially a concern with studies of 9/11-exposed rescue/recovery workers since those cohorts are not sizeable and only approximately 15 percent female. Moreover, the overlap in participation in the studies may limit the interpretation of consistency of findings among the studies. Approximately 20 percent of 9/11-exposed rescue/recovery workers enrolled in the WTC Health Program are also enrolled in the WTC Health Registry. These two cohorts also may be prone to selection bias, because enrollment in the respective programs was voluntary. For the WTC Health Registry cohort, it is possible that differential participation due to race/ethnicity, socioeconomic status, age, or their perception of being affected by the 9/11 attacks, may have occurred. For the rescue/recovery worker cohort enrolled in the WTC Health Program, their health status, including their cancer diagnosis, may have prompted them to enroll. A strength of these studies is that findings are available for both 9/11-exposed rescue/recovery workers as well as survivors.

The relevant studies published to date, and reviewed above, do not provide consistent evidence that uterine cancer, including endometrial cancer, incidence or mortality is elevated among WTC responders and/or survivors. In addition, the studies did not report a dose-response relationship between WTC-related exposures and uterine cancer, including endometrial cancer. Taken together, these studies do not have sufficient quality and quantity to demonstrate a potential to provide a basis for a decision on whether to add uterine cancer, including endometrial cancer, to the List. Accordingly, these studies are not further reviewed.

#### *Administrator Determination*

Upon review of the evidence available in peer-reviewed, published, epidemiological studies and updates regarding uterine cancer, including endometrial cancer, among 9/11-exposed populations, the Administrator has determined that the available evidence does not have the potential to provide a basis for deciding whether to propose adding uterine cancer, including endometrial cancer, to the List. Accordingly, the Administrator has not directed the Program to assess the available evidence using Methods 1, 2, or 3, nor has he directed the Program to request advice from the STAC pursuant to Method 4, discussed above.

The WTC Health Program may consider uterine cancer, including endometrial cancer, to be a condition medically associated with a certified WTC-related health condition in individual cases. Program members who think their uterine or endometrial cancer is a side effect of treatment of a certified WTC-related health condition should ask their WTC Health Program medical provider whether their endometrial cancer might be considered a medically associated health condition.

#### **E. Administrator's Final Decision on Whether to Propose the Addition of Uterine Cancer, Including Endometrial Cancer, to the List**

Pursuant to PHS Act, sec. 3312(a)(6)(B)(iv) and 42 CFR 88.16(a)(2)(iv), the Administrator has determined that insufficient evidence is available to take further action at this time, including proposing the addition of uterine cancer, including endometrial cancer, to the List (pursuant to PHS Act, sec. 3312(a)(6)(B)(ii) and 42 CFR 88.16(a)(2)(ii)) or publishing a determination not to publish a proposed rule in the *Federal Register* (pursuant to PHS Act, sec. 3312(a)(6)(B)(iii) and 42 CFR

88.16(a)(2)(iii)). The Administrator has also determined that requesting a recommendation from the STAC (pursuant to PHS Act, sec. 3312(a)(6)(B)(i) and 42 CFR 88.16(a)(2)(i)) is unwarranted.

For the reasons discussed above, the Petition 023 request to add endometrial cancer to the List of WTC-Related Health Conditions is denied.

#### **F. Approval to Submit Document to the Office of the Federal Register**

The Secretary, HHS, or his designee, the Director, Centers for Disease Control and Prevention (CDC) and Administrator, Agency for Toxic Substances and Disease Registry (ATSDR), authorized the undersigned, the Administrator of the WTC Health Program, to sign and submit the document to the Office of the Federal Register for publication as an official document of the WTC Health Program. Robert Redfield M.D., Director, CDC, and Administrator, ATSDR, approved this document for publication on September 12, 2019.

**John J. Howard,**

*Administrator, World Trade Center Health Program and Director, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Department of Health and Human Services.*

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